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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,199	09/10/2003	Stephen M. Allen	BB1157 US CNT	5569

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EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,199	ALLEN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *search results*.

DETAILED ACTION

1. The finality of the Office action mailed 27 February 2007 is withdrawn in light of the new rejection below.

2. Claims 26-29 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding a SEQ ID NO:18 and constructs and vectors comprising them, does not reasonably provide enablement for nucleic acids encoding a protein with 90% identity to SEQ ID NO:18 and constructs and vectors comprising them. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the rejection set forth in the Office action mailed 27 February 2007. Applicant's arguments filed 28 February 2008 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding a protein with 90% or 95% identity to SEQ ID NO:18 and constructs and vectors comprising them.

The instant specification, however, only provides guidance for cDNA libraries from a number of plants and plant tissues, including wheat developing kernel, and sequencing the inserts from an unknown number of the clones in these libraries (example 1), BLAST analysis of

the cDNA sequences (example 2), identification of clones that have homology to the *Arabidopsis*, potato and corn brittle-1 homologs; the clones include SEQ ID NO:17, which encodes SEQ ID NO:18 (example 3). The specification also provides general guidance for the expression of chimeric genes in monocots (example 4), dicots (example 5), and microbes (example 6).

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:18 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain adenylate translocator activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Nucleic acids encoding proteins with 90% identity to the 433 amino acid long SEQ ID NO:18 would encode proteins with 43 amino acid substitutions, and nucleic acids encoding proteins with 95% identity to SEQ ID NO:18 would encode proteins with 21 amino acid substitutions. The instant specification fails to provide guidance for how to make these nucleic acids.

The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on

enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein.

Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2).

The specification fails to provide an assay for Brittle-1 activity. The specification on pg 6, lines 20-21, references Shannon et al (1998, Plant Physiol. 117:1235-1252). In this reference, ADP-glucose uptake was measured in isolated amyloplasts from *bt-1* mutants (See paragraph spanning pg 1245-1246). The specification fails to teach how to use this method to assay variant nucleic acids. It is possible Applicant envisions transforming bt-1 mutant maize or a yet unidentified wheat equivalent with nucleic acids encoding the variants, isolating the amyloplasts from the transformants, and measuring ADP-glucose uptake. However, it is not clear that this laborious process would even be possible. Sullivan et al (1995, Planta 196:477-484) teach that the full-length maize Brittle-1 coding region could not be expressed in *E. coli* (pg 478, left column, paragraph 3).

Thus, making and analyzing proteins with up to 43 amino acid substitutions that also have adenylate translocator activity would require undue experimentation.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges any experimentation required to make the claimed nucleic acids would be routine (Brief pg 13-14).

This is not found persuasive because the experimentation required for making the variants would be undue, given the lack of teaching of which regions of the protein can tolerate substitutions and given the lack of teachings of an assay.

Applicant urges the quantity of experimentation is low, and sufficient guidance is provided in the specification (Brief pg 14).

This is not found persuasive. The quantity of experimentation is high, as detailed above, and insufficient guidance is provided in the specification, as detailed above.

Applicant urges BT1 is a major protein in amyloplast envelope membranes, and loss results in an 80% reduction in kernel starch; this was studied in A636 and *waxy* kernels (Brief pg 14-15).

This is not found persuasive because this does not provide a means for assaying variant nucleic acids, as detailed above. Sullivan only studied the brittle-1 mutant, and did not assay variant nucleic acids he constructed.

Applicant urges the invention is related to the biotechnical arts in a well-known pathway and the skill level in the art is high (Brief pg 15).

This is not found persuasive because the skill level in the art is unable to assay the claimed nucleic acids.

Applicant urges it is unreasonable for Applicants to provide a cookbook recipe of how to practice the invention; one of skill in the art could use routine methods (Brief pg 15).

This is not found persuasive because the specification fails to provide an assay or teach regions of the protein that can tolerate amino acid substitution.

Applicant urges the number of possible sequences is not the issue (Brief pg 15-16).

This is not found persuasive because they are an issue when the lack of guidance in the specification means that one must practice trail and error experimentation.

Applicant urges the instant situation is similar to *Novozymes*, where 95% homology was ruled as being sufficiently similar to satisfy enablement (Brief pg 16-17).

This is not found persuasive because each case is analyzed on its own merits. 95% homology for a well-studied enzyme like a b-amylase is very different from 95% homology for a protein like brtittle-1 whose function is just being understood.

Applicant urges the novel aspect of the invention is enabled by the specification with the disclosure of SEQ ID NO:18; whether the sequences have brittle-1 activity is irrelevant to novelty (Brief pg 17-18).

This is not found persuasive because whether the sequence have brittle-1 activity is relevant to enablement.

Applicant urges *Kubin* supports Applicant's enablement arguments because the Board found the specification taught how to make variants with 80% identity and any experimentation would be routine; they have provided teachings on pg 15-16 and provided the Shannon assay test (Brief pg 18-19).

This is not found persuasive. The guidance on pg 15-16 is merely general, and not specific to brittle-1 proteins, and the Shannon assay would be laborious for use in testing variants, if it is even possible to do so.

Applicant urges the specification provides written description of the claimed genus further evidence enablement of the claims (Brief pg 19).

This is not found persuasive. Written description and enablement are two different issues. Claims can be enabled and not described and vice versa.

5. Claims 26-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 27 February 2007. Applicant's arguments filed 28 February 2008 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that encoding brittle-1 proteins with 90% identity to SEQ ID NO:18. In contrast, the specification only describes a coding sequence from wheat that comprises SEQ ID NO:17. Applicant does not describe other nucleic acids encompassed by the claims, and the structural and functional features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described nucleic acids that encode a protein with 90% identity to SEQ ID NO:18 within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges their invention conforms to example 14 of the Written Description Guidelines because it teaches procedures for making and assaying the proteins (Brief pg 4-5).

This is not found persuasive. The equivalent example in the Revised Written Description Guidelines is claim 2 of example 11A. Neither the specification nor the prior art describe structures required for the *brittle-1* function. Thus, the specification does not satisfy the written description requirement.

Applicant urges it is well known in the art which amino acid substitutions are conservative, and methods for making such substitutions are well known (Brief pg 5-6).

This is not found persuasive because the specification must also describe the structural features responsible for brittle-1 function, and it does not.

Applicant urges they have provided the *brittle-1* assays from Shannon et al (Brief pg 6).

This is not found persuasive because, as discussed in the enablement rejection, above, this assay is not practical, and it might not even work for assaying variants.

Applicant urges the instant case is distinguishable from *Ex parte Kubin* because the instant specification provides guidance as to which amino acids may be altered and provides a sequence comparison to a known *brittle-1* protein (Brief pg 6-8).

This is not found persuasive because of the inability to assay the nucleic acid.

Applicant urges their invention is distinguished from other genera of brittle-1 proteins by claimed identity to SEQ ID NO:18 (Brief pg 9).

This is not found persuasive because more must be provided, given the functional language.

Applicant urges they have detailed SEQ ID NO:17 and variants with 90% identity to distinguish these brittle-1 genes from the prior art (Brief pg 9-10).

This is not found persuasive. The standard is not distinguishing from the prior art, but distinguishing the structural features of the nucleic acid encoding a protein with the claimed function.

Applicant cites *Invitrogen, Fiers, Faulkner, Wallach, Capon,* and *Enzo* to support their position (Brief pg 10-12).

This is not found persuasive. None of these cases are drawn to nucleic acid encoding proteins, wherein those nucleic acids cannot be assayed in any practical manner.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 26-29 rejected under 35 U.S.C. 103(a) as being unpatentable over Sullivan et al (1991, Plant cell 3:1337-1348) in view of Li et al (1992, J. Biol. Chem. 267:18999-19004).

The claims are broadly drawn to nucleic acids encoding a protein with 90% or 95% identity to SEQ ID NO:18 and expression constructs and vectors comprising them.

Sullivan et al teach the isolation of a vector comprising a genomic nucleic acid encoding the maize Brittle-1 protein (pg 1338, right column, paragraph 1, to pg 1339, right column, paragraph 1). Sullivan et al do not teach nucleic acids that encoding brittle-1 proteins with 90% or 95% identity to SEQ ID NO:18.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the sequence taught by Sullivan et al to isolate brittle-1 homologs from other plants, including wheat, using the maize sequence as a probe, thus isolating a nucleic acid encoding a protein with 90% or 95% identity to SEQ ID NO: 18. A sequence comparison between the maize nucleic acid sequence and the wheat sequence is provided; the regions of identity between the two nucleic acids indicate that such a hybridization would have been successful. One of ordinary skill in the art would have been motivated to do so to better study starch synthesis in endosperm and to study the function of brittle-1. Further, because Li et al teach that brittle-1 has a transit peptide that targets the protein to the inner amyloplast membrane, one of ordinary skill in the art would have been motivated to isolate the wheat homolog to increase the repertoire of such transit peptides to use in expression constructs in plant transformation.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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May 24, 2008

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